



## **Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents**

Downloaded from <http://aidsinfo.nih.gov/guidelines> on 7/22/2014

Visit the AIDSinfo website to access the most up-to-date guideline.

Register for e-mail notification of guideline updates at <http://aidsinfo.nih.gov/e-news>.

## ***Toxoplasma gondii* Encephalitis** (Last updated May 7, 2013; last reviewed May 7, 2013)

---

Toxoplasmic encephalitis (TE) is caused by the protozoan *Toxoplasma gondii*. Disease appears to occur almost exclusively because of reactivation of latent tissue cysts.<sup>1-4</sup> Primary infection occasionally is associated with acute cerebral or disseminated disease.

### **Epidemiology**

Seroprevalence of anti-*Toxoplasma* antibody varies substantially among different geographic locales, with a prevalence of approximately 11% in the United States, versus 50% to 80% in certain European, Latin American, and African countries.<sup>4-6</sup> In the era before antiretroviral therapy (ART), the 12-month incidence of TE was approximately 33% in patients with advanced immunosuppression who were seropositive for *T. gondii* and not receiving prophylaxis with drugs against the disease. A low incidence of toxoplasmosis is seen in patients who are seronegative for *T. gondii*. If patients are truly seronegative, their toxoplasmosis presumably represents one of three possible scenarios:

- 1) Primary infection,
- 2) Re-activation of latent disease in individuals who cannot produce detectable antibodies, *or*
- 3) Testing with insensitive assays.<sup>7,8</sup>

Clinical disease is rare among patients with CD4 T lymphocyte (CD4) cell counts >200 cells/μL. Patients with CD4 counts <50 cells/μL are at greatest risk.<sup>1,3,8,9</sup> Primary infection occurs after eating undercooked meat containing tissue cysts or ingesting oocysts that have been shed in cat feces and sporulated in the environment, a process that takes at least 24 hours. In the United States, eating raw shellfish including oysters, clams, and mussels recently was identified as a novel risk factor for acute infection.<sup>10</sup> Up to 50% of individuals with documented primary infection do not have an identifiable risk factor.<sup>11</sup> The organism is not transmitted through person-to-person contact.

### **Clinical Manifestations**

Among patients with AIDS, the most common clinical presentation of *T. gondii* infection is focal encephalitis with headache, confusion, or motor weakness and fever.<sup>1,3,9</sup> Patients may also present with non-focal manifestations, including only non-specific headache and psychiatric symptoms. Focal neurological abnormalities may be present on physical examination, and in the absence of treatment, disease progression results in seizures, stupor, and coma. Retinochoroiditis, pneumonia, and evidence of other multifocal organ system involvement are rare in patients with AIDS. Computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain will typically show multiple contrast-enhancing lesions in the grey matter of the cortex or basal ganglia, often with associated edema.<sup>1,9,12-14</sup> Toxoplasmosis also can manifest as a single brain lesion or diffuse encephalitis without evidence of focal brain lesions on imaging studies.<sup>15</sup> This latter presentation tends to be rapidly progressive and fatal.

### **Diagnosis**

HIV-infected patients with TE are almost uniformly seropositive for anti-toxoplasma immunoglobulin G (IgG) antibodies.<sup>1,3,9,16</sup> The absence of IgG antibody makes a diagnosis of toxoplasmosis unlikely but not impossible. Anti-toxoplasma immunoglobulin M (IgM) antibodies usually are absent. Quantitative antibody titers are not useful for diagnosis.

Definitive diagnosis of TE requires a compatible clinical syndrome; identification of one or more mass lesions by CT, MRI, or other radiographic testing; and detection of the organism in a clinical sample. On imaging studies, lesions are usually ring-enhancing and have a predilection for the basal ganglia. MRI has sensitivity superior to that of CT studies for radiological diagnosis of TE. Positron emission tomography<sup>13</sup> or single-photon emission computed tomography scanning<sup>14</sup> may be helpful in distinguishing between TE and primary central

nervous system (CNS) lymphoma, but no imaging technique is completely specific. For TE, detection of the organism requires a brain biopsy, which is most commonly performed by a stereotactic CT-guided needle biopsy. Hematoxylin and eosin stains can be used for detection of *T. gondii*, but sensitivity is significantly increased if immunoperoxidase staining is used and if experienced laboratories process the specimens.<sup>17</sup> If safe and feasible, a lumbar puncture should be performed for *T. gondii* polymerase chain reaction (PCR), as well as for cytology, culture, cryptococcal antigen and PCR for *Mycobacterium tuberculosis*, Epstein-Barr Virus (EBV) and JC Virus (JCV), either at initial presentation or subsequently, especially in patients in whom empiric therapy fails. Detection of *T. gondii* by PCR in CSF has high specificity (96%–100%), but low sensitivity (50%), especially once specific anti-toxoplasma therapy has been started.<sup>18–20</sup>

The differential diagnosis of focal neurological disease in patients with AIDS most often includes primary CNS lymphoma and progressive multifocal leucoencephalopathy (PML). In the absence of immune reconstitution inflammatory syndrome (IRIS), PML (but not lymphoma) can be distinguished on the basis of imaging studies. PML lesions typically involve white matter rather than gray matter, are non-contrast enhancing, and produce no mass effect. Less common causes of focal neurologic disease in patients with AIDS include mycobacterial infection (especially tuberculosis [TB]); fungal infection, such as cryptococcosis; Chagas disease; and pyogenic brain abscess, particularly in IV drug abusers.

Most clinicians initially rely on an empiric diagnosis, which can be established as an objective response, documented by clinical and radiographic improvement, to specific anti-*T. gondii* therapy in the absence of a likely alternative diagnosis. Brain biopsy is reserved for patients who fail to respond to specific therapy, although earlier biopsy should be strongly considered if results from imaging, serology, or PCR suggest an etiology other than toxoplasmosis. In patients with contrast-enhancing mass lesions, detection of EBV and JCV by PCR in CSF is highly suggestive of CNS lymphoma<sup>21,22</sup> or PML,<sup>23</sup> respectively.

## Preventing Exposure

HIV-infected individuals should be tested for IgG antibody to *Toxoplasma* soon after they are diagnosed with HIV to detect latent infection with *T. gondii* (**BIII**). They also should be counseled regarding sources of *Toxoplasma* infection, especially if they lack IgG antibody to *Toxoplasma*.

To minimize risk of acquiring toxoplasmosis, HIV-infected individuals should be advised not to eat raw or undercooked meat, including undercooked lamb, beef, pork, or venison, and not to eat raw shellfish including oysters, clams, and mussels (**BIII**). Lamb, beef, venison, and pork should be cooked to an internal temperature of 165°F to 170°F;<sup>24</sup> meat cooked until it is no longer pink inside usually has an internal temperature of 165°F to 170°F, and therefore, from a more practical perspective, satisfies this requirement. To minimize the risk for acquiring toxoplasmosis, HIV-infected individuals should wash their hands after contact with raw meat and after gardening or other contact with soil; they should also wash fruits and vegetables well before eating them raw (**BIII**). Patients who are seronegative and who own cats should be advised to have someone who is HIV-negative and not pregnant change the litter box daily. If they must change the litter box themselves, they should wash their hands thoroughly after doing so (**BIII**). HIV-infected patients also should be encouraged to keep their cats inside and not to adopt or handle stray cats (**BIII**). Cats should be fed only canned or dried commercial food or well-cooked table food, not raw or undercooked meats (**BIII**). Patients do not need to be advised to part with their cats or to have their cats tested for toxoplasmosis (**AII**).

## Preventing Disease

### Indication for Primary Prophylaxis

*Toxoplasma*-seropositive patients who have CD4 counts <100 cells/μL should receive prophylaxis against TE (**AII**).<sup>25,26</sup>

The double-strength-tablet daily dose of trimethoprim-sulfamethoxazole (TMP-SMX), which is the preferred regimen for *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis, is effective against TE and is recommended

(**AII**). TMP-SMX, one double-strength tablet three times weekly, is an alternative (**BIII**). If patients cannot tolerate TMP-SMX, the recommended alternative is dapsone-pyrimethamine plus leucovorin, which is also effective against PCP (**BI**).<sup>27-29</sup> Atovaquone with or without pyrimethamine/leucovorin is active against PCP and also can be considered (**CIII**). Aerosolized pentamidine does not protect against TE and **is not recommended** for antitoxoplasma prophylaxis (**AI**).<sup>25,30</sup>

*Toxoplasma*-seronegative persons who are not taking a PCP prophylactic regimen known to be active against TE, such as aerosolized pentamidine, should be retested for IgG antibody to *Toxoplasma* when their CD4 counts decline to <100 cells/ $\mu$ L to determine whether they have seroconverted and therefore are at risk for TE. Patients who have seroconverted should be administered prophylaxis for TE as previously described (**AII**).

### ***Discontinuing Primary Prophylaxis***

Prophylaxis against TE should be discontinued in adult and adolescent patients receiving ART whose CD4 counts increase to >200 cells/ $\mu$ L for more than 3 months (**AI**). Multiple observational studies<sup>31-33</sup> and two randomized trials<sup>34,35</sup> have reported that primary prophylaxis can be discontinued, with minimal risk for development of TE, in patients receiving ART whose CD4 counts increase from <200 cells/ $\mu$ L to >200 cells/ $\mu$ L for more than 3 months. In these studies, most patients were taking HIV protease inhibitor-containing regimens and the median CD4 count at the time prophylaxis was discontinued was >300 cells/ $\mu$ L. At the time prophylaxis was discontinued, most patients had sustained suppression of plasma HIV RNA levels below the detection limits of available assays; the median follow-up was 7 to 22 months. Patients with CD4 counts of <100 cells/ $\mu$ L are at greatest risk for having TE, but the risk for TE with CD4 counts of 100 to 200 cells/ $\mu$ L has not been studied as rigorously as increases to >200 cells/ $\mu$ L. Thus, the recommendation specifies discontinuing prophylaxis after an increase to >200 cells/ $\mu$ L. When CD4 counts are >200 cells/ $\mu$ L for at least 3 months, primary TE prophylaxis should be discontinued because it adds little value in preventing toxoplasmosis and increases pill burden, potential for drug toxicity and interaction, likelihood of development of drug-resistant pathogens, and cost. Prophylaxis for TE should be reintroduced if the CD4 count decreases to <100 to 200 cells/ $\mu$ L (**AIII**). When a decision to stop PCP prophylaxis is contemplated in patients with CD4 counts of 100 to 200 cells/ $\mu$ L and plasma HIV RNA viral loads below the limits of detection with commercial assays, toxoplasma sero-status should be considered, because seropositive patients may then be at risk for developing TE.

### **Treating Disease**

The initial therapy of choice for TE consists of the combination of pyrimethamine plus sulfadiazine plus leucovorin (**AI**).<sup>2,36-38</sup> Pyrimethamine penetrates the brain parenchyma efficiently even in the absence of inflammation.<sup>39</sup> Leucovorin reduces the likelihood of development of hematologic toxicities associated with pyrimethamine therapy.<sup>40</sup> Pyrimethamine plus clindamycin plus leucovorin (**AI**)<sup>36,37</sup> is the preferred alternative regimen for patients with TE who cannot tolerate sulfadiazine or do not respond to first-line therapy. It does not prevent PCP, therefore additional PCP prophylaxis must be administered when it is used (**AII**) (see discussion under Preventing Recurrence).

In a small (77 patients) randomized trial, TMP-SMX was reported to be effective and better tolerated than pyrimethamine-sulfadiazine.<sup>41</sup> Others have reported similar efficacy in open-label observational studies.<sup>42</sup> TMP-SMX has less *in vitro* activity and experience using this drug to treat toxoplasmosis in developed countries is limited; however, it can be considered an option if there is a valid reason not to use pyrimethamine plus sulfadiazine. (**BI**)

No well-studied options exist for patients who cannot take an oral regimen. No parenteral formulation of pyrimethamine exists and the only widely available parenteral sulfonamide is the sulfamethoxazole component of TMP-SMX. Some specialists will use parenteral TMP-SMX (**BI**) or oral pyrimethamine plus parenteral clindamycin (**CIII**) as initial treatment in severely ill patients who require parenteral therapy.

The following regimens have been shown to be effective in treating TE in at least two nonrandomized, uncontrolled trials, although their relative efficacy compared with the previous regimens is unknown:

atovaquone (with meals or oral nutritional supplements) plus either pyrimethamine plus leucovorin or sulfadiazine or, for patients intolerant of both pyrimethamine and sulfadiazine, as a single agent (**BII**)<sup>43,44,45</sup> (if atovaquone is used alone, clinicians should be aware that the absorption of the drug from patient to patient is highly variable; plasma levels >18.5 µg/mL are associated with an improved response rate but measurements are not routinely available);<sup>44-46</sup> and azithromycin plus pyrimethamine plus leucovorin daily (**CII**).<sup>47,48</sup>

The following regimens have been reported to have activity in treatment of TE in small cohorts of patients or in case reports of one or several patients: clarithromycin plus pyrimethamine (**CIII**);<sup>49</sup> 5-fluorouracil plus clindamycin (**CIII**);<sup>50</sup> dapsone plus pyrimethamine plus leucovorin (**CIII**);<sup>51</sup> and minocycline or doxycycline combined with either pyrimethamine plus leucovorin, sulfadiazine, or clarithromycin (**CIII**).<sup>52,53</sup> Although the clarithromycin dose used in the only published study was 1g twice a day, doses >500 mg have been associated with increased mortality in HIV-infected patients treated for disseminated *Mycobacterium avium* Complex. Doses >500 mg twice a day **should not be used** (**BIII**).

Clinical response to acute therapy occurs in 90% of patients with TE within 14 days of initiation of appropriate anti-toxoplasma treatment.<sup>2</sup> The reasons why some patients fail therapy are not clearly proven; whether such failures are due to poor adherence or to other host factors of antimicrobial resistance has not been well delineated. Acute therapy for TE should be continued for at least 6 weeks, if there is clinical and radiologic improvement (**BII**).<sup>1-4</sup> Longer courses may be appropriate if clinical or radiologic disease is extensive or response is incomplete at 6 weeks. The radiologic goals for treatment include complete resolution of the lesion(s) in terms of size and contrast enhancement, although small scars may persist indefinitely. Adjunctive corticosteroids such as dexamethasone should only be administered to patients with TE when they are clinically indicated to treat a mass effect associated with focal lesions or associated edema (**BIII**). In those treated with corticosteroids, caution may be needed in diagnosing CNS toxoplasmosis on the basis of treatment response, since primary CNS lymphoma may respond clinically and radiographically to corticosteroids alone; these patients should be monitored carefully as corticosteroids are tapered. In addition, corticosteroids should be discontinued as soon as clinically feasible because of their potential to cause immunosuppression. Patients receiving corticosteroids should be monitored closely for development of other opportunistic infections (OIs), including cytomegalovirus retinitis and TB.

Anticonvulsants should be administered to patients with TE who have a history of seizures (**AIII**), but **should not be administered** prophylactically to all patients (**BIII**). Anticonvulsants, if administered, should be continued at least through the period of acute therapy.

### ***Special Considerations with Regard to Starting ART***

There are no data on which to base a recommendation regarding when to start ART in a patient with TE. However, many physicians would initiate ART within 2 to 3 weeks after the diagnosis of toxoplasmosis (**CIII**), based on the significantly lower incidence of AIDS progression or death (a secondary study endpoint) seen in the ART arm of a controlled trial of 282 patients with OIs other than TB (only 5% of whom had toxoplasmosis) who were randomized to early (median 12 days after initiation of OI therapy) versus deferred (median 45 days) initiation of ART.<sup>54</sup>

### ***Monitoring of Response to Therapy and Adverse Events (including IRIS)***

Changes in antibody titers are not useful for monitoring responses to therapy. Patients with TE should be monitored routinely for adverse events and clinical and radiologic improvement (**AIII**). Common pyrimethamine toxicities such as rash, nausea, and bone marrow suppression (neutropenia, anemia, and thrombocytopenia) often can be reversed by increasing the leucovorin dose to 10, 25, or 50 mg 4 times daily (**CIII**).

Common sulfadiazine toxicities include rash, fever, leukopenia, hepatitis, nausea, vomiting, diarrhea, renal insufficiency, and crystalluria. Common clindamycin toxicities include fever, rash, nausea, diarrhea (including pseudomembranous colitis or diarrhea related to *Clostridium difficile* toxin), and hepatotoxicity. Common TMP-SMX toxicities include rash, fever, leukopenia, thrombocytopenia, and hepatotoxicity.



Common atovaquone toxicities include nausea, vomiting, diarrhea, rash, headache, hyperglycemia, and fever. Drug interactions between anticonvulsants and antiretroviral agents should be evaluated carefully; if necessary, doses should be adjusted or alternative anticonvulsants should be used.

IRIS associated with TE has been reported but appears to be rare (~5% in one report).<sup>55-57</sup> Given the rarity of TE-associated IRIS, recommendations for management of such events are difficult to develop.

### ***Managing Treatment Failure***

A brain biopsy should be strongly considered in patients who did not have an initial biopsy prior to therapy and who fail to respond to initial therapy for TE (**BII**) as defined by clinical or radiologic deterioration during the first week despite adequate therapy, or who do not show clinical improvement within 10 to 14 days. A switch to an alternative regimen, as previously described, should be considered for those who undergo brain biopsy and have confirmed histopathologic evidence of TE, or who have a CSF PCR positive for *T. gondii* (**BIII**). In patients who adhere to their regimens, disease recurrence is unusual in the setting of secondary maintenance therapy after an initial clinical and radiographic response.

## **Preventing Recurrence**

### ***When to Start Secondary Prophylaxis***

Patients who have completed initial therapy for TE should be given suppressive therapy with secondary prophylaxis or chronic maintenance therapy (**AI**)<sup>36,37</sup> until immune reconstitution occurs as a consequence of ART, in which case treatment discontinuation is indicated. The combination of pyrimethamine plus sulfadiazine plus leucovorin is highly effective as suppressive therapy for patients with TE (**AI**) and provides protection against PCP (**AII**). Although sulfadiazine is routinely dosed as a four-times-a-day regimen, a pharmacokinetic study suggests bioequivalence for the same total daily dose when given either twice or four times a day,<sup>58</sup> and limited clinical experience suggests that twice-daily dosing is effective.<sup>59</sup> Pyrimethamine plus clindamycin is commonly used as suppressive therapy for patients with TE who cannot tolerate sulfa drugs (**BI**). Because of the high failure rate observed with lower doses,<sup>36</sup> a dose of 600 mg clindamycin every 8 hours is recommended (**CIII**). Because this regimen does not provide protection against PCP (**AII**), an additional agent, such as aerosol pentamidine, must be used. Atovaquone with or without pyrimethamine or sulfadiazine is also active against both TE<sup>45,46</sup> and PCP<sup>60</sup> (**BII**), but is substantially more expensive. A small, uncontrolled study in patients who had been receiving ART for a median of 13 months suggested that TMP-SMX could be used as a suppressive regimen to reduce pill burden.<sup>61</sup>

Although there are no data on the long-term suppressive efficacy of the other alternative regimens noted above, clinicians might consider using these agents in unusual situations in which the recommended agents cannot be administered (**CIII**).

### ***When to Stop Secondary Prophylaxis***

Adult and adolescent patients receiving secondary prophylaxis or chronic maintenance therapy for TE are at low risk for recurrence of TE when they have successfully completed initial therapy for TE, remain asymptomatic with regard to signs and symptoms of TE, and have an increase in their CD4 counts to >200 cells/ $\mu$ L after ART that is sustained for more than 6 months.<sup>32,35,62,63</sup> Discontinuing chronic maintenance therapy in such patients is a reasonable consideration, although occasional recurrences have been reported. The recommendation is based on results in a limited number of patients from observational studies and one randomized clinical trial and inference from more extensive cumulative data indicating the safety of discontinuing secondary prophylaxis for other OIs during advanced disease (**BI**). As part of the evaluation to determine whether discontinuation of therapy is appropriate, some specialists recommend obtaining an MRI of the brain to assess for resolution of brain lesions.

Secondary prophylaxis (chronic maintenance therapy) for TE should be reintroduced if the CD4 count decreases to <200 cells/ $\mu$ L (**AIII**).

## Special Considerations During Pregnancy

Documentation of baseline maternal *T. gondii* serologic status (IgG) should be obtained in HIV-infected women who are pregnant. Primary *T. gondii* infection can typically be distinguished from chronic infection with the use of multiple serologic assays, including IgG, IgM, IgA, and IgE antibodies; IgG avidity; and the differential agglutination tests.<sup>64,65</sup> Pregnant HIV-infected women with suspected or confirmed primary *T. gondii* infection during pregnancy should be managed in consultation with a maternal-fetal medicine specialist or another appropriate specialist who can perform specialized laboratory testing (**BIII**)<sup>65,66</sup> (e.g., the Palo Alto Medical Foundation Toxoplasmosis Serology Laboratory; Palo Alto, CA; <http://www.pamf.org/serology/> at 650-853-4828 and [toxolab@pamf.org](mailto:toxolab@pamf.org); and the National Collaborative Chicago-based Congenital Toxoplasmosis Study; Chicago, IL; <http://www.uchospitals.edu/specialties/infectious-diseases/toxoplasmosis/> at 773-834-4131 and [rmcleod@midway.uchicago.edu](mailto:rmcleod@midway.uchicago.edu)).

Toxoplasmosis diagnostic considerations are the same in pregnant women as in non-pregnant women.

Indications for treatment of *T. gondii* during pregnancy should be based on confirmed or suspected symptomatic disease in the mother and the risk of transmission of the parasite from mother to fetus. Maternal treatment of TE should be the same as in non-pregnant adults (**BIII**), including pyrimethamine plus sulfadiazine plus leucovorin (**AI**).<sup>2,36-38</sup> This regimen is also believed to prevent mother-to-child transmission of *T. gondii* and it may be therapeutic for affected fetuses.<sup>65</sup>

Although pyrimethamine has been associated with birth defects in animals, human data have not suggested an increased risk for defects, therefore, it can be administered to pregnant women after the first trimester.<sup>67-71</sup> Similarly, sulfadiazine appears safe in pregnancy.<sup>72</sup> A randomized, controlled trial published in 1956 found that premature infants receiving prophylactic penicillin/sulfisoxazole were at significantly higher risk of mortality (specifically kernicterus), compared with infants who received oxytetracycline.<sup>73</sup> Because of these findings, some clinicians are concerned about the risk of neonatal kernicterus in the setting of maternal use of sulfa (including sulfadiazine) near delivery, although there are no studies published to date link late third-trimester maternal sulfa use and neonatal death or kernicterus.

The preferred alternative regimen for patients with TE who are unable to tolerate or who fail to respond to first-line therapy is pyrimethamine plus clindamycin plus leucovorin (**AI**).<sup>36,37</sup> Clindamycin is Food and Drug Administration Pregnancy Category B and considered safe throughout pregnancy. Atovaquone may be used if indicated. While there are limited data on atovaquone safety in humans, preclinical studies have not demonstrated toxicity.<sup>68</sup>

Although perinatal transmission of *T. gondii* normally occurs only with acute infection in the immunocompetent host, case reports have documented transmission with reactivation of chronic infection in HIV-infected women with severe immunosuppression.<sup>70,74</sup> Pregnant HIV-infected women who have evidence of primary toxoplasmic infection or active toxoplasmosis, including TE, should be evaluated and managed during pregnancy in consultation with appropriate specialists (**BIII**). Detailed ultrasound examination of the fetus specifically evaluating for hydrocephalus, cerebral calcifications, and growth restriction should be done for HIV-infected women with suspected primary or symptomatic reactivation of *T. gondii* during pregnancy (**AIII**).<sup>65</sup> Amniocentesis does not appear to increase the risk of perinatal HIV transmission, particularly in women receiving HAART.<sup>75</sup> Therefore, PCR of amniotic fluid can be considered during gestation in pregnant women on ART with serologic evidence of acquired infection, and also for women with ultrasound findings suggestive of fetal *T. gondii* infection (**BIII**).<sup>65</sup> Because the risk for transmission with chronic infection appears low, routine fetal evaluation for infection with amniocentesis is not indicated.

Pediatric-care providers should be informed about HIV-infected mothers who have suspected or confirmed *T. gondii* infection to allow evaluation of their neonates for evidence of congenital infection (**AIII**).

TMP-SMX can be administered for primary prophylaxis against TE as described for PCP (**AIII**). The risks of TMP-SMX in the first trimester, as discussed for PCP, must be balanced against the risk of TE. Secondary

prophylaxis should be provided, using the same indications as for non-pregnant women. As noted above, pyrimethamine and sulfadiazine are considered safe in pregnancy. Clindamycin may be substituted for sulfadiazine for sulfa-intolerant patients. Dapsone appears to cross the placenta.<sup>76,77</sup> Over the past several decades, dapsone (used for primary prophylaxis) has been used safely in pregnancy to treat leprosy, malaria, and various dermatologic conditions.<sup>77,78</sup> With long-term therapy, there is a risk of mild maternal hemolysis and a potential—although extremely low—risk of hemolytic anemia in exposed fetuses with G6PD deficiency.<sup>79</sup>

Because the odds of perinatal HIV transmission decrease by 6% to 8% per week of ART, clinicians should consider immediate initiation of ART for pregnant women who are diagnosed with TE and not yet on ART **(BIII)**.<sup>80,81</sup> Because in-utero transmission of HIV is associated with HIV viremia at 30 (+/- 4) weeks' gestation, immediate ART is particularly indicated for women who are diagnosed with TE in the third trimester **(AIII)**.<sup>82</sup> When providing preconception care for HIV-infected women receiving TE prophylaxis, providers should discuss the option of deferring pregnancy until TE prophylaxis can be safely discontinued **(BIII)**.

## Recommendations for Preventing and Treating *Toxoplasma gondii* Encephalitis (page 1 of 2)

### Preventing 1st Episode of *Toxoplasma gondii* Encephalitis (Primary Prophylaxis)

#### Indications for Initiating Primary Prophylaxis:

- *Toxoplasma* IgG positive patients with CD4 count <100 cells/mm<sup>3</sup> **(AII)**
- *Toxoplasma* seronegative patients receiving a PCP prophylaxis regimen not active against toxoplasmosis should have *toxoplasma* serology retested if CD4 count declines to <100 cells/mm<sup>3</sup> **(CIII)**
- Prophylaxis against toxoplasmosis should be initiated if seroconversion occurred **(AII)**

**Note:** All the recommended regimens for preventing 1st episode of toxoplasmosis are also effective in preventing PCP.

#### Preferred Regimen:

- TMP-SMX 1 DS PO daily **(AII)**

#### Alternative Regimens:

- TMP-SMX 1 DS PO TIW **(BIII)**, or
- TMP-SMX SS PO daily **(BIII)**, or
- Dapsone<sup>a</sup> 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly **(BI)**, or
- (Dapsone<sup>a</sup> 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly **(BI)**, or
- Atovaquone<sup>b</sup> 1500 mg PO daily **(CIII)**, or
- (Atovaquone<sup>b</sup> 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily **(CIII)**

#### Indication for Discontinuing Primary Prophylaxis:

- CD4 count >200 cells/mm<sup>3</sup> for >3 months in response to ART **(AI)**

#### Indication for Restarting Primary Prophylaxis:

- CD4 count <100 to 200 cells/mm<sup>3</sup> **(AIII)**

### Treating *Toxoplasma gondii* Encephalitis

#### Preferred Regimen **(AI)**:

- Pyrimethamine 200 mg PO once, followed by dose based on body weight:
  - Body weight ≤60 kg: pyrimethamine 50 mg PO daily + sulfadiazine 1000 mg PO q6h + leucovorin 10–25 mg PO daily (can increase to 50 mg daily or BID)
  - Body weight >60 kg: pyrimethamine 75 mg PO daily + sulfadiazine 1500 mg PO q6h + leucovorin 10–25 mg PO daily (can increase to 50 mg daily or BID)

#### Alternative Regimens:

- Pyrimethamine (leucovorin)<sup>c</sup> plus clindamycin 600 mg IV or PO q6h **(AI)**; preferred alternative for patients intolerant of sulfadiazine or who do not respond to pyrimethamine-sulfadiazine; must add additional agent for PCP prophylaxis, or
- TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) (IV or PO) BID **(BI)**, or



## Recommendations for Preventing and Treating *Toxoplasma gondii* Encephalitis (page 2 of 2)

- Atovaquone<sup>b</sup> 1500 mg PO BID + pyrimethamine (leucovorin)<sup>c</sup> **(BII)**, *or*
- Atovaquone<sup>b</sup> 1500 mg PO BID + sulfadiazine<sup>d</sup> **(BII)**, *or*
- Atovaquone<sup>b</sup> 1500 mg PO BID **(BII)**, *or*
- Pyrimethamine (leucovorin)<sup>c</sup> plus azithromycin 900–1200 mg PO daily **(CII)**

### Total Duration for Treating Acute Infection:

- At least 6 weeks **(BII)**; longer duration if clinical or radiologic disease is extensive or response is incomplete at 6 weeks

### **Chronic Maintenance Therapy for *Toxoplasma gondii* Encephalitis**

#### Preferred Regimen:

- Pyrimethamine 25–50 mg PO daily + sulfadiazine 2000–4000 mg PO daily (in 2 to 4 divided doses) + leucovorin 10–25 mg PO daily **(AI)**

#### Alternative Regimen:

- Clindamycin 600 mg PO q8h + (pyrimethamine 25–50 mg + leucovorin 10–25 mg) PO daily **(BI)**; must add additional agent to prevent PCP **(AII)**, *or*
- TMP-SMX DS 1 tablet BID **(BII)**, *or*
- Atovaquone<sup>b</sup> 750–1500 mg PO BID + (pyrimethamine 25 mg + leucovorin 10 mg) PO daily, *or*
- Atovaquone<sup>b</sup> 750–1500 mg PO BID + sulfadiazine 2000–4000 mg PO daily (in 2 to 4 divided doses) **(BII)**, *or*
- Atovaquone<sup>b</sup> 750–1500 mg PO BID **(BII)**

#### Discontinuing Chronic Maintenance Therapy:

- Successfully completed initial therapy, remain asymptomatic of signs and symptoms of TE, and CD4 count >200 cells/mm<sup>3</sup> for >6 months in response to ART **(BI)**

### **Criteria for Restarting Secondary Prophylaxis/Chronic Maintenance**

- CD4 count <200 cells/mm<sup>3</sup> **(AIII)**

### **Other Considerations:**

- Adjunctive corticosteroids (e.g., dexamethasone) should only be administered when clinically indicated to treat a mass effect associated with focal lesions or associated edema **(BIII)**; discontinue as soon as clinically feasible.
- Anticonvulsants should be administered to patients with a history of seizures **(AIII)** and continued through at least through the period of acute treatment; anticonvulsants **should not be used** as seizure prophylaxis **(BIII)**.

<sup>a</sup> Whenever possible, patients should be tested for G6PD deficiency before administering dapsone. Alternative agent should be used if the patient is found to have G6PD deficiency.

<sup>b</sup> Atovaquone should be taken with meals or nutritional supplement to ensure adequate oral absorption.

<sup>c</sup> Pyrimethamine and leucovorin doses: Same as doses listed in Preferred Regimen for Acute Infection

<sup>d</sup> Sulfadiazine dose: Same as weight-based dose listed in Preferred Regimen for Acute Infection

**Key to Acronyms:** ART = antiretroviral therapy; BID = twice daily; CD4 = CD4 T lymphocyte cell; DS = double strength; G6PD = glucose-6-phosphate dehydrogenase; IgG = immunoglobulin G; IV = intravenous; PCP = *Pneumocystis* Pneumonia; PO = orally; q(n)h = every “n” hours; SS = single strength; TE = toxoplasmic encephalitis; TIW = three times a week; TMP-SMX = trimethoprim-sulfamethoxazole

## References

1. Luft BJ, Conley F, Remington JS, et al. Outbreak of central-nervous-system toxoplasmosis in western Europe and North America. *Lancet*. Apr 9 1983;1(8328):781-784. Available at <http://www.ncbi.nlm.nih.gov/pubmed/6132129>.
2. Luft BJ, Hafner R, Korzun AH, et al. Toxoplasmic encephalitis in patients with the acquired immunodeficiency syndrome. Members of the ACTG 077p/ANRS 009 Study Team. *N Engl J Med*. Sep 30 1993;329(14):995-1000. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8366923>.

3. Wong B, Gold JW, Brown AE, et al. Central-nervous-system toxoplasmosis in homosexual men and parenteral drug abusers. *Ann Intern Med.* Jan 1984;100(1):36-42. Available at <http://www.ncbi.nlm.nih.gov/pubmed/6691657>.
4. Israelski DM, Chmiel JS, Poggensee L, Phair JP, Remington JS. Prevalence of Toxoplasma infection in a cohort of homosexual men at risk of AIDS and toxoplasmic encephalitis. *J Acquir Immune Defic Syndr.* Apr 1993;6(4):414-418. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8455146>.
5. Mathews WC, Fullerton SC. Use of a clinical laboratory database to estimate Toxoplasma seroprevalence among human immunodeficiency virus-infected patients. Overcoming bias in secondary analysis of clinical records. *Archives of pathology & laboratory medicine.* Aug 1994;118(8):807-810. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8060230>.
6. Jones JL, Kruszon-Moran D, Sanders-Lewis K, Wilson M. Toxoplasma gondii infection in the United States, 1999-2004, decline from the prior decade. *Am J Trop Med Hyg.* Sep 2007;77(3):405-410. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17827351>.
7. Abgrall S, Rabaud C, Costagliola D, Clinical Epidemiology Group of the French Hospital Database on HIV. Incidence and risk factors for toxoplasmic encephalitis in human immunodeficiency virus-infected patients before and during the highly active antiretroviral therapy era. *Clin Infect Dis.* Nov 15 2001;33(10):1747-1755. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11595976>.
8. Leport C, Chene G, Morlat P, et al. Pyrimethamine for primary prophylaxis of toxoplasmic encephalitis in patients with human immunodeficiency virus infection: a double-blind, randomized trial. ANRS 005-ACTG 154 Group Members. Agence Nationale de Recherche sur le SIDA. AIDS Clinical Trial Group. *J Infect Dis.* Jan 1996;173(1):91-97. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8537688>.
9. Luft BJ, Brooks RG, Conley FK, McCabe RE, Remington JS. Toxoplasmic encephalitis in patients with acquired immune deficiency syndrome. *JAMA.* Aug 17 1984;252(7):913-917. Available at <http://www.ncbi.nlm.nih.gov/pubmed/6748191>.
10. Jones JL, Dargelas V, Roberts J, Press C, Remington JS, Montoya JG. Risk factors for Toxoplasma gondii infection in the United States. *Clin Infect Dis.* Sep 15 2009;49(6):878-884. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19663709>.
11. Boyer KM, Holfels E, Roizen N, et al. Risk factors for Toxoplasma gondii infection in mothers of infants with congenital toxoplasmosis: Implications for prenatal management and screening. *Am J Obstet Gynecol.* Feb 2005;192(2):564-571. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15696004>.
12. Kupfer MC, Zee CS, Colletti PM, Boswell WD, Rhodes R. MRI evaluation of AIDS-related encephalopathy: toxoplasmosis vs. lymphoma. *Magnetic resonance imaging.* 1990;8(1):51-57. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2325518>.
13. Pierce MA, Johnson MD, Maciunas RJ, et al. Evaluating contrast-enhancing brain lesions in patients with AIDS by using positron emission tomography. *Ann Intern Med.* Oct 15 1995;123(8):594-598. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7677300>.
14. Ruiz A, Ganz WI, Post MJ, et al. Use of thallium-201 brain SPECT to differentiate cerebral lymphoma from toxoplasma encephalitis in AIDS patients. *AJNR. American journal of neuroradiology.* Nov 1994;15(10):1885-1894. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7863938>.
15. Gray F, Gherardi R, Wingate E, et al. Diffuse "encephalitic" cerebral toxoplasmosis in AIDS. Report of four cases. *J Neurol.* Jul 1989;236(5):273-277. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2760644>.
16. Derouin F, Leport C, Pueyo S, et al. Predictive value of Toxoplasma gondii antibody titres on the occurrence of toxoplasmic encephalitis in HIV-infected patients. ANRS 005/ACTG 154 Trial Group. *AIDS.* Nov 1996;10(13):1521-1527. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8931787>.
17. Conley FK, Jenkins KA, Remington JS. Toxoplasma gondii infection of the central nervous system. Use of the peroxidase-antiperoxidase method to demonstrate toxoplasma in formalin fixed, paraffin embedded tissue sections. *Hum Pathol.* Aug 1981;12(8):690-698. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7026410>.
18. Novati R, Castagna A, Morsica G, et al. Polymerase chain reaction for Toxoplasma gondii DNA in the cerebrospinal fluid of AIDS patients with focal brain lesions. *AIDS.* Dec 1994;8(12):1691-1694. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7888118>.
19. Cinque P, Scarpellini P, Vago L, Linde A, Lazzarin A. Diagnosis of central nervous system complications in HIV-infected patients: cerebrospinal fluid analysis by the polymerase chain reaction. *AIDS.* Jan 1997;11(1):1-17. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9110070>.
20. Mesquita RT, Ziegler AP, Hiramoto RM, Vidal JE, Pereira-Chiocola VL. Real-time quantitative PCR in cerebral

- toxoplasmosis diagnosis of Brazilian human immunodeficiency virus-infected patients. *Journal of medical microbiology*. Jun 2010;59(Pt 6):641-647. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20150319>.
21. Antinori A, Ammassari A, De Luca A, et al. Diagnosis of AIDS-related focal brain lesions: a decision-making analysis based on clinical and neuroradiologic characteristics combined with polymerase chain reaction assays in CSF. *Neurology*. Mar 1997;48(3):687-694. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9065549>.
  22. Antinori A, De Rossi G, Ammassari A, et al. Value of combined approach with thallium-201 single-photon emission computed tomography and Epstein-Barr virus DNA polymerase chain reaction in CSF for the diagnosis of AIDS-related primary CNS lymphoma. *J Clin Oncol*. Feb 1999;17(2):554-560. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10080599>.
  23. Koralnik IJ, Boden D, Mai VX, Lord CI, Letvin NL. JC virus DNA load in patients with and without progressive multifocal leukoencephalopathy. *Neurology*. Jan 15 1999;52(2):253-260. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9932940>.
  24. US Department of Health & Human Services. FoodSafety.gov: your gateway to federal food safety information. Available at <http://www.foodsafety.gov>. Accessed March 26, 2013.
  25. Carr A, Tindall B, Brew BJ, et al. Low-dose trimethoprim-sulfamethoxazole prophylaxis for toxoplasmic encephalitis in patients with AIDS. *Ann Intern Med*. Jul 15 1992;117(2):106-111. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1351371>.
  26. Miro JM, Murray HW, Katlama C. Toxoplasmosis. In: Dolin R, H. M, M. S, eds. *AIDS Therapy*. Third ed. Philadelphia: Churchill Livingstone; 2008:659-681.
  27. Podzamecz D, Salazar A, Jimenez J, et al. Intermittent trimethoprim-sulfamethoxazole compared with dapsone-pyrimethamine for the simultaneous primary prophylaxis of Pneumocystis pneumonia and toxoplasmosis in patients infected with HIV. *Ann Intern Med*. May 15 1995;122(10):755-761. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7717598>.
  28. Opravil M, Hirschel B, Lazzarin A, et al. Once-weekly administration of dapsone/pyrimethamine vs. aerosolized pentamidine as combined prophylaxis for Pneumocystis carinii pneumonia and toxoplasmic encephalitis in human immunodeficiency virus-infected patients. *Clin Infect Dis*. Mar 1995;20(3):531-541. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7756472>.
  29. Girard PM, Landman R, Gaudebout C, et al. Dapsone-pyrimethamine compared with aerosolized pentamidine as primary prophylaxis against Pneumocystis carinii pneumonia and toxoplasmosis in HIV infection. The PRIO Study Group. *N Engl J Med*. May 27 1993;328(21):1514-1520. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8479488>.
  30. Bozzette SA, Finkelstein DM, Spector SA, et al. A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. NIAID AIDS Clinical Trials Group. *N Engl J Med*. Mar 16 1995;332(11):693-699. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7854375>.
  31. Dworkin MS, Hanson DL, Kaplan JE, Jones JL, Ward JW. Risk for preventable opportunistic infections in persons with AIDS after antiretroviral therapy increases CD4+ T lymphocyte counts above prophylaxis thresholds. *J Infect Dis*. Aug 2000;182(2):611-615. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10915098>.
  32. Kirk O, Lundgren JD, Pedersen C, Nielsen H, Gerstoft J. Can chemoprophylaxis against opportunistic infections be discontinued after an increase in CD4 cells induced by highly active antiretroviral therapy? *AIDS*. Sep 10 1999;13(13):1647-1651. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10509565>.
  33. Furrer H, Opravil M, Bernasconi E, Telenti A, Egger M. Stopping primary prophylaxis in HIV-1-infected patients at high risk of toxoplasma encephalitis. Swiss HIV Cohort Study. *Lancet*. Jun 24 2000;355(9222):2217-2218. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10881897>.
  34. Mussini C, Pezzotti P, Govoni A, et al. Discontinuation of primary prophylaxis for Pneumocystis carinii pneumonia and toxoplasmic encephalitis in human immunodeficiency virus type I-infected patients: the changes in opportunistic prophylaxis study. *J Infect Dis*. May 2000;181(5):1635-1642. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10823763>.
  35. Miro JM, Lopez JC, Podzamecz D, et al. Discontinuation of primary and secondary Toxoplasma gondii prophylaxis is safe in HIV-infected patients after immunological restoration with highly active antiretroviral therapy: results of an open, randomized, multicenter clinical trial. *Clin Infect Dis*. Jul 1 2006;43(1):79-89. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16758422>.
  36. Katlama C, De Wit S, O'Doherty E, Van Glabeke M, Clumeck N. Pyrimethamine-clindamycin vs. pyrimethamine-

- sulfadiazine as acute and long-term therapy for toxoplasmic encephalitis in patients with AIDS. *Clin Infect Dis*. Feb 1996;22(2):268-275. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8838183>.
37. Dannemann B, McCutchan JA, Israelski D, et al. Treatment of toxoplasmic encephalitis in patients with AIDS. A randomized trial comparing pyrimethamine plus clindamycin to pyrimethamine plus sulfadiazine. The California Collaborative Treatment Group. *Ann Intern Med*. Jan 1 1992;116(1):33-43. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1727093>.
  38. Leport C, Raffi F, Matheron S, et al. Treatment of central nervous system toxoplasmosis with pyrimethamine/sulfadiazine combination in 35 patients with the acquired immunodeficiency syndrome. Efficacy of long-term continuous therapy. *Am J Med*. Jan 1988;84(1):94-100. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3337134>.
  39. Leport C, Meulemans A, Robine D, Dameron G, Vilde JL. Levels of pyrimethamine in serum and penetration into brain tissue in humans. *AIDS*. Sep 1992;6(9):1040-1041. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1388895>.
  40. Van Delden C, Hirschel B. Folinic acid supplements to pyrimethamine-sulfadiazine for Toxoplasma encephalitis are associated with better outcome. *J Infect Dis*. May 1996;173(5):1294-1295. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8627092>.
  41. Torre D, Casari S, Speranza F, et al. Randomized trial of trimethoprim-sulfamethoxazole versus pyrimethamine-sulfadiazine for therapy of toxoplasmic encephalitis in patients with AIDS. Italian Collaborative Study Group. *Antimicrob Agents Chemother*. Jun 1998;42(6):1346-1349. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9624473>.
  42. Beraud G, Pierre-Francois S, Foltzer A, et al. Cotrimoxazole for treatment of cerebral toxoplasmosis: an observational cohort study during 1994-2006. *Am J Trop Med Hyg*. Apr 2009;80(4):583-587. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19346380>.
  43. Chirgwin K, Hafner R, Leport C, et al. Randomized phase II trial of atovaquone with pyrimethamine or sulfadiazine for treatment of toxoplasmic encephalitis in patients with acquired immunodeficiency syndrome: ACTG 237/ANRS 039 Study. AIDS Clinical Trials Group 237/Agence Nationale de Recherche sur le SIDA, Essai 039. *Clin Infect Dis*. May 1 2002;34(9):1243-1250. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11941551>.
  44. Kovacs JA. Efficacy of atovaquone in treatment of toxoplasmosis in patients with AIDS. The NIAID-Clinical Center Intramural AIDS Program. *Lancet*. Sep 12 1992;340(8820):637-638. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1355212>.
  45. Torres RA, Weinberg W, Stansell J, et al. Atovaquone for salvage treatment and suppression of toxoplasmic encephalitis in patients with AIDS. Atovaquone/Toxoplasmic Encephalitis Study Group. *Clin Infect Dis*. Mar 1997;24(3):422-429. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9114194>.
  46. Katlama C, Mouthon B, Gourdon D, Lapierre D, Rousseau F. Atovaquone as long-term suppressive therapy for toxoplasmic encephalitis in patients with AIDS and multiple drug intolerance. Atovaquone Expanded Access Group. *AIDS*. Sep 1996;10(10):1107-1112. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8874627>.
  47. Saba J, Morlat P, Raffi F, et al. Pyrimethamine plus azithromycin for treatment of acute toxoplasmic encephalitis in patients with AIDS. *Eur J Clin Microbiol Infect Dis*. Nov 1993;12(11):853-856. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8112357>.
  48. Jacobson JM, Hafner R, Remington J, et al. Dose-escalation, phase I/II study of azithromycin and pyrimethamine for the treatment of toxoplasmic encephalitis in AIDS. *AIDS*. Mar 30 2001;15(5):583-589. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11316995>.
  49. Fernandez-Martin J, Leport C, Morlat P, Meyohas MC, Chauvin JP, Vilde JL. Pyrimethamine-clarithromycin combination for therapy of acute Toxoplasma encephalitis in patients with AIDS. *Antimicrob Agents Chemother*. Oct 1991;35(10):2049-2052. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1836943>.
  50. Dhiver C, Milandre C, Poizot-Martin I, Drogoul MP, Gastaut JL, Gastaut JA. 5-Fluoro-uracil-clindamycin for treatment of cerebral toxoplasmosis. *AIDS*. Jan 1993;7(1):143-144. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8442914>.
  51. Derouin F, Piketty C, Chastang C, Chau F, Rouveix B, Pocidalo JJ. Anti-Toxoplasma effects of dapsone alone and combined with pyrimethamine. *Antimicrob Agents Chemother*. Feb 1991;35(2):252-255. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2024957>.
  52. Lacassin F, Schaffo D, Perronne C, Longuet P, Leport C, Vilde JL. Clarithromycin-minocycline combination as salvage therapy for toxoplasmosis in patients infected with human immunodeficiency virus. *Antimicrob Agents Chemother*. Jan



- 1995;39(1):276-277. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7695324>.
53. Hagberg L, Palmertz B, Lindberg J. Doxycycline and pyrimethamine for toxoplasmic encephalitis. *Scandinavian journal of infectious diseases*. 1993;25(1):157-160. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8460343>.
  54. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One*. 2009;4(5):e5575. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19440326>.
  55. Pfeffer G, Prout A, Hooge J, Maguire J. Biopsy-proven immune reconstitution syndrome in a patient with AIDS and cerebral toxoplasmosis. *Neurology*. Jul 28 2009;73(4):321-322. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19636053>.
  56. Tremont-Lukats IW, Garciarena P, Juarbe R, El-Abassi RN. The immune inflammatory reconstitution syndrome and central nervous system toxoplasmosis. *Ann Intern Med*. May 5 2009;150(9):656-657. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19414855>.
  57. Martin-Blondel G, Alvarez M, Delobel P, et al. Toxoplasmic encephalitis IRIS in HIV-infected patients: a case series and review of the literature. *J Neurol Neurosurg Psychiatry*. Jun 2011;82(6):691-693. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20660912>.
  58. Jordan MK, Burstein AH, Rock-Kress D, et al. Plasma pharmacokinetics of sulfadiazine administered twice daily versus four times daily are similar in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother*. Feb 2004;48(2):635-637. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14742225>.
  59. Podzamczar D, Miro JM, Ferrer E, et al. Thrice-weekly sulfadiazine-pyrimethamine for maintenance therapy of toxoplasmic encephalitis in HIV-infected patients. Spanish Toxoplasmosis Study Group. *Eur J Clin Microbiol Infect Dis*. Feb 2000;19(2):89-95. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10746493>.
  60. El-Sadr WM, Murphy RL, Yurik TM, et al. Atovaquone compared with dapsone for the prevention of *Pneumocystis carinii* pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. Community Program for Clinical Research on AIDS and the AIDS Clinical Trials Group. *N Engl J Med*. Dec 24 1998;339(26):1889-1895. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9862944>.
  61. Duval X, Pajot O, Le Moing V, et al. Maintenance therapy with cotrimoxazole for toxoplasmic encephalitis in the era of highly active antiretroviral therapy. *AIDS*. Jun 18 2004;18(9):1342-1344. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15362670>.
  62. Soriano V, Dona C, Rodriguez-Rosado R, Barreiro P, Gonzalez-Lahoz J. Discontinuation of secondary prophylaxis for opportunistic infections in HIV-infected patients receiving highly active antiretroviral therapy. *AIDS*. Mar 10 2000;14(4):383-386. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10770540>.
  63. Bertschy S, Opravil M, Cavassini M, et al. Discontinuation of maintenance therapy against toxoplasma encephalitis in AIDS patients with sustained response to anti-retroviral therapy. *Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. Jul 2006;12(7):666-671. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16774564>.
  64. Montoya JG. Laboratory diagnosis of *Toxoplasma gondii* infection and toxoplasmosis. *J Infect Dis*. Feb 15 2002;185 Suppl 1:S73-82. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11865443>.
  65. Montoya JG, Remington JS. Management of *Toxoplasma gondii* infection during pregnancy. *Clin Infect Dis*. Aug 15 2008;47(4):554-566. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18624630>.
  66. Mitchell CD, Erlich SS, Mastrucci MT, Hutto SC, Parks WP, Scott GB. Congenital toxoplasmosis occurring in infants perinatally infected with human immunodeficiency virus 1. *Pediatr Infect Dis J*. Jul 1990;9(7):512-518. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2371084>.
  67. Peters PJ, Thigpen MC, Parise ME, Newman RD. Safety and toxicity of sulfadoxine/pyrimethamine: implications for malaria prevention in pregnancy using intermittent preventive treatment. *Drug Saf*. 2007;30(6):481-501. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17536875>.
  68. Nosten F, McGready R, d'Alessandro U, et al. Antimalarial drugs in pregnancy: a review. *Current drug safety*. Jan 2006;1(1):1-15. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18690910>.
  69. Wong SY, Remington JS. Toxoplasmosis in pregnancy. *Clin Infect Dis*. Jun 1994;18(6):853-861; quiz 862. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8086543>.
  70. Dunn CS, Beyer C, Kienny MP, et al. High viral load and CD4 lymphopenia in rhesus and cynomolgus macaques

- infected by a chimeric primate lentivirus constructed using the env, rev, tat, and vpu genes from HIV-1 Lai. *Virology*. Sep 15 1996;223(2):351-361. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8806570>.
71. Deen JL, von Seidlein L, Pinder M, Walraven GE, Greenwood BM. The safety of the combination artesunate and pyrimethamine-sulfadoxine given during pregnancy. *Trans R Soc Trop Med Hyg*. Jul-Aug 2001;95(4):424-428. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11579889>.
  72. Baskin CG, Law S, Wenger NK. Sulfadiazine rheumatic fever prophylaxis during pregnancy: does it increase the risk of kernicterus in the newborn? *Cardiology*. 1980;65(4):222-225. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7388849>.
  73. Andersen DH, Blanc WA, Crozier DN, Silverman WA. A difference in mortality rate and incidence of kernicterus among premature infants allotted to two prophylactic antibacterial regimens. *Pediatrics*. Oct 1956;18(4):614-625. Available at <http://www.ncbi.nlm.nih.gov/pubmed/13370229>.
  74. Low incidence of congenital toxoplasmosis in children born to women infected with human immunodeficiency virus. European Collaborative Study and Research Network on Congenital Toxoplasmosis. *Eur J Obstet Gynecol Reprod Biol*. Sep 1996;68(1-2):93-96. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8886688>.
  75. Mandelbrot L, Jasseron C, Ekoukou D, et al. Amniocentesis and mother-to-child human immunodeficiency virus transmission in the Agence Nationale de Recherches sur le SIDA et les Hepatites Virales French Perinatal Cohort. *Am J Obstet Gynecol*. Feb 2009;200(2):160 e161-169. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18986640>.
  76. Zuidema J, Hilbers-Modderman ES, Merkus FW. Clinical pharmacokinetics of dapsone. *Clinical pharmacokinetics*. Jul-Aug 1986;11(4):299-315. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3530584>.
  77. Brabin BJ, Eggelte TA, Parise M, Verhoeff F. Dapsone therapy for malaria during pregnancy: maternal and fetal outcomes. *Drug Saf*. 2004;27(9):633-648. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15230645>.
  78. Newman RD, Parise ME, Slutsker L, Nahlen B, Steketee RW. Safety, efficacy and determinants of effectiveness of antimalarial drugs during pregnancy: implications for prevention programmes in Plasmodium falciparum-endemic sub-Saharan Africa. *Tropical medicine & international health: TM & IH*. Jun 2003;8(6):488-506. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12791054>.
  79. Thornton YS, Bowe ET. Neonatal hyperbilirubinemia after treatment of maternal leprosy. *Southern medical journal*. May 1989;82(5):668. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2717998>.
  80. Hoffman RM, Black V, Technau K, et al. Effects of highly active antiretroviral therapy duration and regimen on risk for mother-to-child transmission of HIV in Johannesburg, South Africa. *J Acquir Immune Defic Syndr*. May 1 2010;54(1):35-41. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20216425>.
  81. Warszawski J, Tubiana R, Le Chenadec J, et al. Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort. *AIDS*. Jan 11 2008;22(2):289-299. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18097232>.
  82. Tubiana R, Le Chenadec J, Rouzioux C, et al. Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/ml at delivery: a case-control study nested in the French perinatal cohort (EPF-ANRS CO1). *Clin Infect Dis*. Feb 15 2010;50(4):585-596. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20070234>.